REMARKS

1. Overview of Claim Amendments

Claim 1 has been amended, without prejudice or disclaimer, to limit the antibody to the elected species, i.e., an antibody capable of binding to an epitope within the sequence consisting of amino acid residues 20-44 according to SEQ ID NO:1. Said sequence is labeled as "hHBP (20-44)" for further reference.

Claim 1, as examined, was directed to a composition "comprising an antibody against hHBP (SEQ ID NO:1) or a fragment of said antibody...."

As amended, the composition is one comprising a monoclonal antibody which binds hHBP (SEQ ID NO:1) or a compound comprising an hHBP-binding fragment of said antibody...." The change from "against" to "which binds" was to avoid any implication that the antibody had to be made by immunizing an animal with hHBP per se.

A fragment comprising the recited epitope could be used as the immunogen, or the antibody could be made recombinantly, see P20, L32-35.

The term "fragment" was too narrow because the application clearly contemplates compounds in which an antibody fragment as defined by P13, L19-20 is combined with another moiety, as in the case of a single chain antibody (P14, L34-P15, L7), a diabody (P15, L9-16), a chimeric antibody (P16, L29-P17, L2), or a humanized antibody (P18, L10-35). Hence it was replaced with "a compound comprising an hHBP-binding fragment of said antibody". Of course, a "compound comprising a... fragment" may be simply the fragment.

Also, the original claim failed to specify that the fragment retained binding activity, and the amended claim remedies this.

We have also deleted, without prejudice or disclaimer, the reference to homologues of hHBP. However, an antibody which binds hHBP may also be capable of binding a homologue of hHBP.

At pp. 34-37, applicants describe a whole blood screening assay which examined the effects of F19A5B1, F19A5B4, pHBP, hHBP

(20-44) and the bacterial products PCW (purified cell wall) or PGN (peptidoglycan) on IL-6 secretion as evidenced by IL-6 levels in whole blood. The basal IL-6 level was low (10.4, 13.0 pg/ml), and this was not affected by F19A5B4 (168 μg/ml) alone (10.4, 14.3). The combination of F19A5B1 (168 μg/ml), pHBP (25 μg/ml) and PCW (90 μg/ml), increased IL-6 to 4755.4. If the F19A5B1 were replaced with F19A5B4, IL-6 decreased to 6.5 (a 731.6-fold change). (Table 1).

The specification comments at P36, L1-8:

> From table 1 it appears that the monoclonal antibody produced by clone F19A5B1 (fusion No19 well A5 sub-cloned and well B1 selected) enhanced the IL-6 secretion when added alone, and also stimulated the IL-6 production when added together with PCW and pHBP in the whole blood assay described above. From the table it also appears that the monoclonal antibody F19A5B4, obtained from well 4 in the same sub-cloning of F19A5, had the opposite effect resulting in inhibition of the IL-6 production when added either alone of in the presence of PCW and pHBP.

With hHBP (20-44) we had the following results, all extracted from Table 2:

IL-6 level in Whole Blood (pg/ml)				
hHBP (20-44)	by itself	+PGN (250 μg/ml)	also +F19A5B4 (168 μg/ml)	hHBP + F19A5B4 without PGN
360 μg/ml	510.5 366.6	27639.4 23178.0	3635.7 2615.7	317.4 255.7
180	122.7 142.7	19289.1 22415.3	730.1 1006.1	80.7 70.6

90	60.7 51.9	14668.9 8109.7	332.7 145.0	56.8 60.7
45		10619.0 9783.6	60.1	17.3 16.4

F19A5B4 thus induced a minimum reduction in the IL-6 levels induced by the hHBP (20-44)/PGN combination of 6.375 fold (23178/2615.7) at the 360 level 19.17-fold (19289.1/1006.1) at the 180 level, 24375-fold (8109.7/332.7) at the 90 level, and 162.78-fold (9783.6/60.1) at the 45 level.

F19A5B4 induced a minimum reduction in IL-6 levels induced by hHBP (20-44) alone of 1.155-fold (366.6/317.4) at the 360 level, 1.52-fold (122.7/80.7) at the 180 level.

The specification comments at P37, first paragraph after the table:

> From table 2 it appears that human 20-44 peptide acetylated in the N terminal and amidated in the C terminal respectively enhanced the IL-6 secretion when added alone and also enhanced the IL-6 secretion when added together with PGN. However, the monoclonal antibody F19A5B4 inhibits these effects of the peptide.

Claim 1, as amended, with basis as stated above, requires that the antibody have a minimum capability to inhibit IL-6 production in response to hHBP in combination with a bacterial product. Claim 58 specifies that the bacterial product is PGN. Claim 59 requires a minimum inhibition of IL-6 production induced by hHBP (20-44) in absence of any bacterial product, and 60, in absence of PGN.

2. Election/Restriction (OA §2)

Claim 1 has been amended to limit it to antibodies which bind residues 20-44 of SID1. This distinguishes Flodgaard, and

hence the dependent method claims should be rejoined pursuant to MPEP 821.04.

3. Claim Objections (OA §6)

Claim 19 has been amended to strike "as defined in claims 10-23".

4. Written Description (OA §7-8)

The Examiner questions whether there is written description for "all 'homologoues of hHBP' as targets of the claimed antibody. The Examiner concedes that there is written description of hHBP (SEQ ID NO:1) as well as of its homologues pHBP (SEQ ID NO:588) and hNEL (SEQ ID NO:589). The Examiner contends that the disclosure of hHBP and these two homologues is insufficient to support the asserted genus absent explicit description of the "structural features shared by these disclosed species". The examiner also contends that there is, for homologues of hHBP, a lack of any art-recognized correlation between structure and function.

First of all, we respectfully state that the art is in effective possession of the common features of these three sequences because the sequences are explicitly disclosed and it is within ordinary skill in the art to align these sequences by means of pairwise or multiple sequence alignment software.

Such alignment is suggested by P1, L35-P2, L4:

> Sequence analysis of HBP has revealed that the protein bears many similarities to serine proteases, which are important in inflammatory processes, e.g. neutrophil elastase (47% homology) or protease 3 (43% homology), however HBP lacks protease activity due to mutations of two of three amino acids in the highly conserved catalytic triad. The structure of HBP appears from WO 89/08666 and Flodgaard et al., 1991 (Eur. J. Biochem. 197:535-547).

The identification of pHBP as "highly homologous" (P1, L28-33) necessarily required sequence comparison with hBP.

In In re Wallach, 378 F.3d 1330, 71 USPQ2d 1939 (Fed. Cir. 2004), relating to claims to a DNA molecule comprising a coding sequence for TBP-II, the Federal Circuit conceded that, by the 1980s, the molecular biology art had reached the point that knowledge of the complete amino acid sequence of a protein puts the skilled worker in possession of the entire sequence of DNA sequences which encodes that protein, even though the sequence of the wild type gene is not known, and it refused to impose on applicants the burden of listing the possible coding sequences. In like manner, in this case, it is straightforward to align the three sequences and identify residues which are fully conserved (aligned residues are identical) or partially conserved (aligned residues are identical or similar, note that a concept of similarity is inherent in the scoring matrix used to score alignments).

Secondly, we call to the Examiner's attention that the specification teaches that there is an important epitope within amino acids 20-44 of hHBP (P3, L11-13; P10, L1-9) and that claim 1, as now amended, requires binding to amino acids 20-44 of hHBP. Thus, applicants teach that there is a correlation between whether the homologue conserves AAs 20-44 of hHBP, and whether the claimed antibody will bind to that analogue.

Finally, we remind the examiner that there is no requirement in the claim that the "homologue" retain any "function" of hBP other than immunological recognition by the claimed antibody. As generally known in the art, antibodies can recognize quite short peptides, such as 6 amino acids or even smaller, and these epitopes can be mutated and still be recognized. This essentially renders irrelevant Attwood and Skolnick, regarding possibly inaccuracies in correlating structure to biological function.

Hence, we respectfully submit that claim 1, as amended, enjoys written description for homologues of hHBP.

Nonetheless, to expedite prosecution, we have amended claim 1 to avoid reference to homologues. The claimed hHBP-binding

antibody may of course still bind homologues, too.

5. Enablement (OA §9)

A parallel rejection for enablement is made. It is respectfully submitted that it is within ordinary skill to use the sequence of pHBP, or of AAs 20-44 of hHBP, as a query sequence in a sequence database search to identify homologues of hHBP. In any event, as previously explained, the claim no longer refers to homologues.

6. Enablement Deposit (OA §11)

Claims 6 and 24 are rejected on the ground that cell clone F19A5B4 is required to practice those claims and there has been no showing that it is (1) known or readily and available to the public, (2) available by a disclosed, repeatable process, or (3) available from a depository, the deposit satisfying 37 CFR 1.84 et seq.

The antibody F19A5B4 is deposited as ECACC 03090302 according to the claims of US Publ. Appl. 2007 0269437 and WO2005/028512.

The specification has been amended to recite the accession number, the date of the deposit, and the name and address of ECACC.

Applicants hereby state that the deposit was made under the Budapest Treaty and all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent on this patent application.

A copy of the deposit receipt is enclosed.

7. Anticipation (OA §13)

Claims 1, 3, 7, 10, 11, 12, 13, 18, 19, 22, 26, 27 and 29 stand rejected as anticipated by Flodgaard et al.

With regard to claim 3, which requires that the antibody bind AAs 20-44 of SID1, the examiner argues:

> Given that Flodgaard et al. teach a polyclonal antibody that binds hHBP, and that polyclonal antibodies are known to bind multiple epitopes, at least one of the antibodies in the composition comprising the polyclonal antibody as taught by the prior art would necessarily bind the epitope within the sequence consisting of amino acid residues 20-44 of hHBP set forth in SEQ ID NO:1.

We respectfully submit that this inference is an insufficient basis for a holding of inherent anticipation. While it is known in the art that a polyclonal antibody will comprise individual antibody molecules which recognize different epitopes, there is no guarantee that a polyclonal antibody will recognize all epitopes of a protein, and hence no guarantee that a polyclonal antibody will recognize AAs 20-44 of hHBP.

The general rule concerning inherent anticipation is that the allegedly inherent feature must be certain to be present in view of the explicit features. See Ex parte Levy, 17 USPQ2d 1461, 1464 (BPAI 1990) ("inherent characteristic necessarily flows" from prior art teachings); Glaxo Inc. v. Novopharm Ltd., 29 USPQ2d 1126 (EDNC 1993), aff'd 34 USPQ2d 1565 (Fed. Cir. 1995) (allegedly inherent result must "invariably" happen); Electro Medical Systems, S.A. v. Cooper Life Sciences, Inc., 32 USPQ2d 1017, 1020 (Fed. Cir. 1994) (that a thing "may result" is insufficient); Motorola, Inc. v. Interdigital Technology Corp., 930 F. Supp. 952, 970 (D. Del. 1996); Marion Merrell Dow Inc. v. Geneva Pharmaceuticals, 33 USPQ2d 1673, 1677 (D. Col. 1994); Hughes Aircraft Co. v. United States, 8 USPQ2d 1580, 1583 (Claims Ct. 1988) (in anticipation-by-inherency cases, the element must "flow undeniably and irrefutably from the express disclosures"); Ethyl Molded Products Co. v. Betts Package, Inc., 9 USPQ2d 1001, 1032-3 (E.D. Ky. 1988) (doctrine requires "certainty"; "probabilities are not sufficient"); Phillips Petroleum Co. v. U.S. Steel Corp., 6 USPQ2d 1065, 1076-77 n. 12 (D. Del. 1987), aff'd 9 USPQ2d 1461 (Fed. Cir. 1989) ("anticipation...cannot be predicated on mere conjecture").

In any event, claim 1 has been amended to require that the antibody is a monoclonal antibody.

8. Obviousness

8.1. Claims 1, 3, 4, 7, 10-13, 18, 19, 22, 26, 27 and 29 stand rejected as obvious over Pereira in view of Flodgaard.

Pereira teaches that hHBP[1] (20-44) has bactericidal activity, see col. 4, lines 64-66, col. 35, lines 21 to col. 36, line 2, and Figs. 15 and 16. Pereira also teaches that hHBP (20-44) can neutralize LPS activity, see col. 36, lines 13-21 and Fig. 17.

Pereira teaches that antibodies "specific against CAP37 protein or bioactive peptides derived from CAP37 or specific against CAP37 protein/peptide fusion proteins" can be produced (col. 36, lines 23-26). The Examples which follow are written in present tense and it is thus unclear whether they were actually practiced. The only disclosed utility for the antibodies is to "detect the presence and amount of CAP37 and/or CAP37 peptides", e.g., "to screen patients for diagnostic purposes".

There is no recognition that hHBP (20-44) stimulates IL-6 production or that an hHBP (20-44)-binding antibody can inhibit such IL-6 production, as now required by claim 1.

Hence, there is no motivation to find an hHBP (20-44) binding antibody with those characteristics, and no reasonable expectation in the prior art that an anti hHBP (20-44) binding antibody will have those characteristics.

8.2. The examiner concedes that cell clone F19A5B4 is free of the prior art (OA §16). Should the examiner determine that amended claim 1 does not distinguish the art, applicants would

[1] "CAP37".

be willing to consider limiting the main claim to F19A5B4 and hHBP-binding antibodies produced by derivatives of clone F19A5B4.

Respectfully submitted,

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Enclosure
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